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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte SHOHEI KOIDE

Appeal 2009-1912
Application 09/903,412
Technology Center 1600

Decided[1]: June 9, 2009

Before ERIC GRIMES, RICHARD M. LEBOVITZ, and
JEFFREY N. FREDMAN, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a modified Fibronectin type III molecule. We have jurisdiction under 35 U.S.C. § 6(b). We reverse and enter a new ground of rejection.

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[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, begins to run from the decided date shown on this page of the decision. The time period does not run from the Mail Date (paper delivery) or Notification Date (electronic delivery).

Statement of the Case

The Claims

Claims 1, 4, 7, 8, and 54-63 are on appeal. We will focus on claim 1, which is representative and reads as follows:

> 1. A modified fibronectin type III (Fn3) molecule comprising a stabilizing mutation of at least one residue involved in an unfavorable electrostatic interaction as compared to a wild-type Fn3, wherein the stabilizing mutation is a substitution of at least one of Asp 7, Asp 23 or Glu 9 with another amino acid residue.

The prior art

The Examiner relies on the following prior art references to show unpatentability:

Lipovsek et al. US 6,818,418 B1 Nov. 16, 2004

Koide WO 98/56915 A2 Dec. 17, 1998

Spector et al., *Rational Modification of Protein Stability by the Mutation of Charged Surface Residues*, 39 BIOCHEMISTRY 872-879 (2000).

The issue

The Examiner rejected claims 1, 4, 7, 8, and 54-63 under 35 U.S.C. § 103(a) as being obvious over Koide, Lipovsek, and Spector (Ans. 4-6).

The Examiner finds that "[e]ach of Koide or Lipovsek teaches stable modified Fn3. However each of these references does not teach that the regions containing e.g., amino acids 7, 9 or 23 are involved in an unfavorable electrostatic interaction, as claimed" (Ans. 5). The Examiner finds that "it would have been obvious to one having ordinary skill in the art at the time the invention was made to determine whether amino acid

residues at e.g., 1-9 or 21-31 of the Fn region of Lipovsek or Koide is involved in an unfavorable electrostatic interactions as taught by Spector" (Ans. 6).

Appellant contends "[t]he Examiner acknowledges that neither Koide nor Lipovsek teaches that the regions of Fn3 containing amino acids 7, 9 and 23 are involved in an unfavorable electrostatic interaction. Applicant respectfully submits that Spector does not remedy the deficiencies of Koide and Lipovsek" (Reply Br. 11).

In view of these conflicting positions, we frame the obviousness issue before us as follows:

Did the Examiner err in finding it obvious to modify Asp7, Asp23 or Glu9 on the Fibronectin type III scaffolds of Koide and Lipovsek based upon the teachings of Spector?

Findings of Fact (FF)

1. Koide teaches "a fibronectin type III (Fn3) polypeptide monobody comprising a plurality of Fn3 B-strand domain sequences that are linked to a plurality of loop region sequences" (Koide 6, ll. 12-14).

2. Koide teaches that "[o]ne or more of the monobody loop region sequences of the Fn3 polypeptide vary by deletion, insertion or replacement of at least two amino acids from the corresponding loop region sequences in wild-type Fn3" (Koide 6, ll. 14-17).

3. Koide teaches that "the loop regions of the monobody comprise amino acid residues . . . from 22 to 30 inclusive in a BC loop" (Koide 6, ll. 20-22).

4. Koide teaches that a "nucleic acid phage display library having seven variegated [randomly mutated] residues (residues number 78-84) in the FG loop and five variegated residues (residue number 26-30) in the BC loop was prepared" (Koide 35, ll. 25-27).

5. Lipovsek teaches "a protein that includes a fibronectin type III domain having at least one randomized loop" (Lipovsek, col. 2, ll. 32-34).

6. Lipovsek teaches that the "three loops of ^{10}Fn3 corresponding to the antigen-binding loops of the IgG heavy chain run between amino acid residues 21-31, 51-56, and 76-88" (Lipovsek, col. 8, ll. 18-20).

7. Lipovsek teaches that for the "human ^{10}Fn3 sequence, this analysis indicates that, at a minimum, amino acids 1-9, 44-50, 61-54 [sic], 82-94 (edges of beta sheets); 19, 21, 30-46 (even), 79-65 (odd) (solvent-accessible faces of both beta sheets); 21-31, 51-56, 76-88 (CDR-like solvent-accessible loops); . . . may be randomized to evolve new or improved compound- binding proteins" (Lipovsek, col. 9, ll. 24-32).

8. Spector "focuses on the peripheral subunit-binding domain, derived from the dihydrolipoamide acetyltransferase component . . . of the pyruvate dehydrogenase multienzyme complex from *Bacillus stearothermophilus*" (Spector 873, col. 1).

9. Spector teaches that "[t]his study provides a clear demonstration that alleviating unfavorable surface interactions can increase the stability of proteins" (Spector 879, col. 1).

10. Spector teaches that "[a]lthough the substitutions described in this paper would not serve this protein well *in vivo*," apparently because the substitutions were in biologically active domains, "the methodology could

nevertheless be applied to other proteins if care is taken to avoid residues involved in catalysis or intermolecular interactions" (Spector 879, col. 1).

Principles of Law

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The Supreme Court has recently emphasized that "the [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007).

"To differentiate between proper and improper applications of 'obvious to try,' this court outlined two classes of situations where 'obvious to try' is erroneously equated with obviousness under § 103. In the first class of cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009) (*citing In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)).

"In such circumstances, where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness." *Id.*

Analysis

Lipovsek and Koide teach randomly screening Fibronectin type III polypeptides at a variety of positions within the peptide sequence (FF 1-7). Spector, in analyzing an unrelated protein, teaches that stabilization of proteins by modifying their sequence is desirable, but provides no specific guidance on selecting residues to be modified in Fibronectin type III (FF 8-9). Spector also suggests that the residue selection may be difficult, noting "the substitutions described in this paper would not serve this protein well in vivo, [but] the methodology could nevertheless be applied to other proteins if care is taken to avoid residues involved in catalysis or intermolecular interactions" (Spector 879, col. 1; FF 10).

In *Kubin*, the court made clear that "where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness." *Kubin*, 561 F.3d at 1359. This rejection is such a situation, where the prior art gives an immense number of possible mutations in the Fibronectin type III molecule including more than 70 different amino acids which may be mutated, potentially to any of the other 19 amino acids[2] (*see* FF 7). Lipovsek, Koide, or Spector do not provide any guidance on which parameters were critical and no direction on which of these mutations is likely to be successful (FF 1-10).

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[2] We note that 19^{70} is equal to 3.25×10^{89} different possibilities.

Unlike *Kubin*, where performing the detailed methodology of cloning would necessarily result in obtaining a molecule within the genus of nucleic acids being claimed, there is no predictable expectation that performing the random screening methods of Lipovsek or Koide would predictably, or even likely, result in polypeptides with mutations at positions 7, 9 or 23 of the Fibronectin type III molecule. Further, even if such polypeptides were obtained, there is no predictable or even minimally likely expectation that the mutations would result in stabilization of the Fibronectin type III molecule as recited in the claim.

We are not persuaded by the Examiner's finding that "[i]t would be within the ordinary skill in the art at the time the invention was made to choose other residues at e.g., position 7 as taught by Lipovsek" (Ans. 10). The Examiner has not explained why information regarding positions in the peripheral subunit-binding domain of pyruvate dehydrogenase taught by Spector has any relevance whatsoever to Fibronectin type III, which is an entirely different protein.

Additionally, however, the Examiner has not established, and we do not find, that the ordinary artisan would have predictably modified positions 7, 9, or 23 of the Fibronectin type III protein in order to obtain a stabilizing mutation. The Examiner has provided no evidence that mutations at any of these three positions would have predictably or reasonably have been expected to have this property, nor has the Examiner presented any other reason to select any of these three positions from the 70 positions disclosed by Lipovsek as mutation targets (FF 7).

Conclusion of Law

The Examiner erred in finding it obvious to modify Asp7, Asp23 or Glu9 on the Fibronectin type III scaffolds of Koide and Lipovsek based upon the teachings of Spector.

New Ground of Rejection

35 U.S.C. § 102(e)

Under the provisions of 37 CFR § 41.50(b), we enter the following new ground of rejection: claims 1, 4, 7, 8, and 54-63 are rejected under 35 U.S.C. § 102(e) as anticipated by Lipovsek.

Findings of Fact (FF)

11. The Specification teaches that "[t]he invention specifically relates to the generation of both nucleic acid and polypeptide libraries encoding the molecular scaffolding of a modified Fibronectin Type III (Fn3) molecule" (Spec. 1, ll. 13-15).

12. The Specification teaches that a "stabilizing mutation is defined herein as a modification or change in the amino acid sequence of the Fn3 molecule, such as a substitution of one amino acid for another, that increases the melting point of the molecule [Tm] by more than 0.1°C as compared to a molecule that is identical except for the change" (Spec. 6, ll. 20-24).

13. The Specification teaches that a mutation of the Asp residue at position 7 for Asparagine resulted in increased Tm (Spec. 37, l. 25 to Spec. 38, l. 1).

14. The Specification teaches that "mutations at Glu 9 and/or Asp 23 also enhance the stability of Fn3. Furthermore, mutations at one or more of these three residues can be combined" (Spec. 38, ll. 11-13).

15. The Specification teaches that "[o]ne or more of the monobody loop region sequences of the Fn3 polypeptide vary by deletion, insertion or replacement of at least two amino acids from the corresponding loop region sequences in wild-type Fn3" (Spec. 7, ll. 6-8).

16. The Specification teaches the sequence of Fibronectin type III in Figure 2, which is reproduced below:

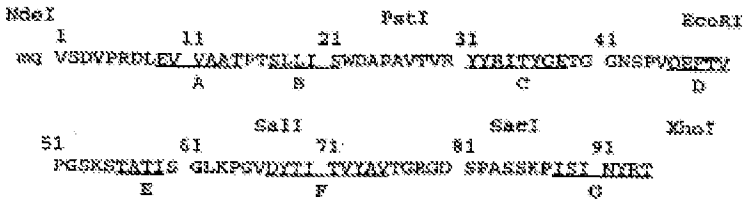
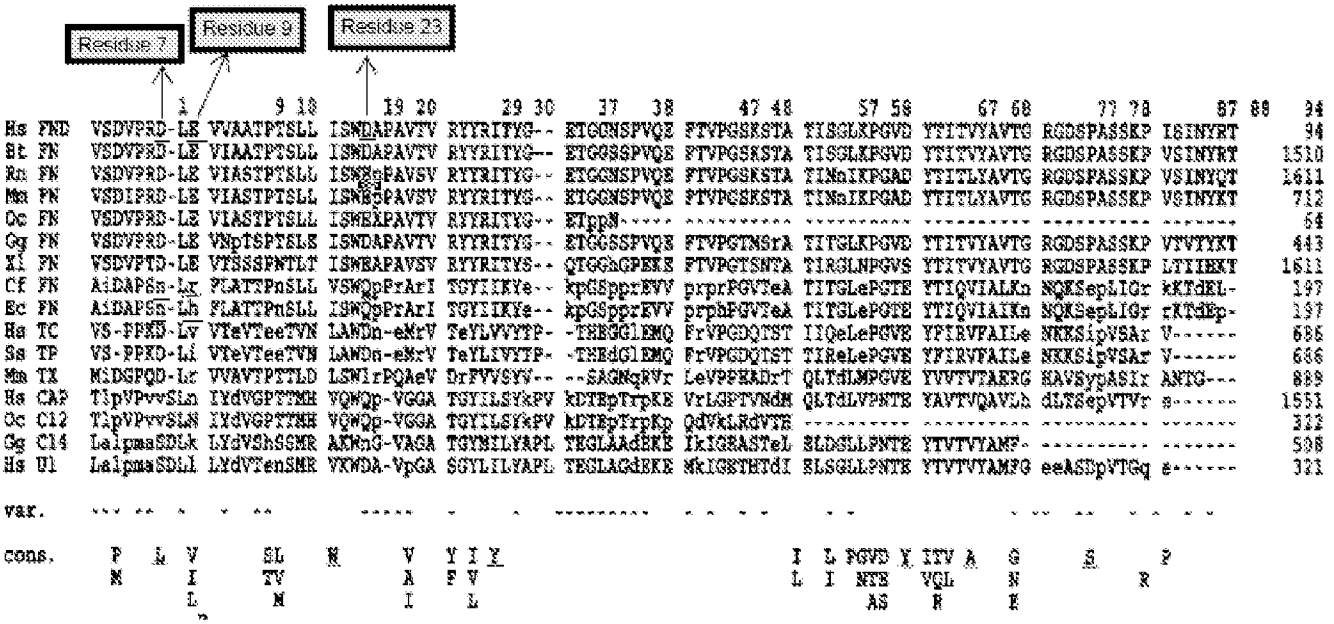


FIG. 2

"Figure 2. Amino acid sequence (SEQ ID NO:110) and restriction sites of the synthetic Fn3 gene" (Spec. 12, ll. 17-18).

17. Lipovsek teaches an alignment of Fibronectin type III sequences in Figure 4, reproduced below with annotations which identify the locations of positions 7, 9 and 23 on the Fibronectin type III molecule:



"FIG. 4 is a graph illustrating a sequence alignment between fibronectin type III protein domain and related protein domains" (Lipovsek, col. 6, ll. 31-33).

18. Lipovsek teaches a Canis familiaris (Cf) sequence which is a Fibronectin type III molecule with a substitution of Asp 7 by neutral Asparagine, a substitution of Glu 9 by positively charged Arginine and a substitution of Asp 23 by Glutamine relative to the wild type human Fibronectin type III sequence (*see* Lipovsek, Figure 4, 8th line ("Cf") in alignment; FF 16).

19 Lipovsek teaches another sequence, RN, in which the Fibronectin type III molecule has a substitution of Asp 23 for Glutamic acid relative to the human fibronectin wild type sequence (*see* Lipovsek, Figure 4, 3rd line in alignment; FF 16).

20. Lipovsek teaches another sequence, HS CAP, in which the Fibronectin type III molecule has a substitution of Glu 9 by asparagine

relative to the human fibronectin wild type sequence (*see* Lipovsek, Figure 4, 13th line in alignment; FF 16).

Principles of Law

"[T]he PTO gives a disputed claim term its broadest reasonable interpretation during patent prosecution". *In re Bigio*, 381 F.3d 1320, 1324 (Fed. Cir. 2004). The court recognizes the fairness of reading claims broadly "before a patent is granted [since] the claims are readily amended as part of the examination process." *Burlington Indus. v. Quigg*, 822 F.2d 1581, 1583 (Fed. Cir. 1987). "Thus, a patent applicant has the opportunity and responsibility to remove any ambiguity in claim term meaning by amending the application". *Bigio*, 381 F.3d at 1324. Applying the broadest reasonable interpretation to claims also "serves the public interest by reducing the possibility that claims, finally allowed, will be given broader scope than is justified." *In re Am. Acad. of Sci. Tech. Ctr.*, 367 F.3d 1359, 1364 (Fed. Cir. 2004).

"A rejection for anticipation under section 102 requires that each and every limitation of the claimed invention be disclosed in a single prior art reference." *In re Paulsen*, 30 F.3d 1475, 1478-79 (Fed. Cir. 1994); *see Karsten Manufacturing Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1383 (Fed. Cir. 2001) ("Invalidity on the ground of 'anticipation' requires lack of novelty of the invention as claimed … that is, all of the elements and limitations of the claim must be shown in a single prior reference, arranged as in the claim.").

"Whether the rejection is based on 'inherency' under 35 U.S.C. § 102, on 'prima facie obviousness' under 35 U.S.C. § 103, jointly or alternatively,

the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products". *In re Best*, 562 F.2d 1252, 1255 (CCPA 1977). "Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product." *Id.*

Analysis

Claim 1 requires a "modified" Fibronectin type III molecule. The Specification does not directly define "modified" (FF 11), but discloses that a "stabilizing mutation is defined herein as a modification or change in the amino acid sequence of the Fn3 molecule, such as a substitution of one amino acid for another" (Spec. 6, ll. 20-24; FF 12). Also, the Specification states that "[o]ne or more of the monobody loop region sequences of the Fn3 polypeptide vary by deletion, insertion or replacement of at least two amino acids from the corresponding loop region sequences in wild-type Fn3" (Spec. 7, ll. 6-8; FF 15). Therefore, the word "modified" is reasonably interpreted in light of the Specification as representing a Fibronectin type III molecule in which there are one or more changes or substitutions in the amino acid sequence relative to the human wild type sequence.

Claim 1 also requires that at least one of Asp 7, Asp 23, or Glu 9 be substituted with another amino acid, which the claim indicates functions as a "stabilizing mutation" (*see* claim 1; FF 13). Dependent claims 4 and 7 specifically identify replacement of Asp 7 or Asp 23 with asparagine as a mutation within the scope of claim 1 (*see* claims 4 and 7).

Lipovsek teaches a human Fibronectin type III sequence which is identical to that disclosed in the Specification (FF 16-17).

Lipovsek also teaches Fibronectin type III sequences which are "modified" relative to the human sequence (FF 18-19). Specifically, Lipovsek teaches a Canis familiaris (Cf) sequence which is a Fibronectin type III molecule with a substitution of Asp 7 by Asparagine, a mutation of Glu 9 by Arginine and a substitution of Asp 23 by Glutamine relative to the wild type human FND (Fibronectin type III domain) sequence among other sequence differences (*see* Lipovsek, Figure 4, 8th line in alignment; FF 17-18). Lipovsek also teaches another sequence, RN, in which the Fibronectin type III molecule has a substitution of Asp 23 by Glutamic acid relative to the human FND wild type sequence (*see* Lipovsek, figure 4, 3rd line in alignment; FF 17, 19). Lipovsek also teaches another sequence, HS CAP, in which the Fibronectin type III molecule has a substitution of Glu 9 by asparagine relative to the human FND wild type sequence (*see* Lipovsek, Figure 4, 13th line in alignment; FF 17, 20).

The Cf, RN, and HS CAP sequences are reasonably interpreted as modified Fibronectin type III molecules with substitutions which would reasonably be believed as inherently stabilizing based upon the teachings of the Specification (FF 12-14).

With regard to claims 4, 55, 57-59, 61, and 63, Lipovsek teaches the Cf Fibronectin type III sequence with a neutral asparagine at the position of Asp 7 (FF 18).

With regard to claims 7, 8 and 57, Lipovsek teaches both the Rn and Cf Fibronectin type III sequences with substitutions of one other amino acid residue at Asp 7, Asp 23, and Glu 9 (FF 18-19).

With regard to claims 54 and 56, Lipovsek teaches a Cf Fibronectin type III sequence in which the Glu 9 is substituted with a positively charged arginine residue (FF 18).

With regard to claims 55 and 58-60, Lipovsek teaches a Cf Fibronectin type III sequence in which the Asp 23 is substituted with a neutral glutamine residue (FF 18).

With regard to claim 62, Lipovsek teaches a Hs CAP Fibronectin type III sequence in which the Glu 9 is substituted with asparagine (FF 20).

In particular regarding the functional requirement that the mutation is a "stabilizing" mutation, we find that since the mutations disclosed by Lipovsek are identical to those required by the claims, the mutations would reasonably be expected to inherently function as "stabilizing" mutations in the absence of evidence to the contrary (FF 16-19). *See In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990) ("[W]hen the PTO shows sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.")

Conclusion of Law

Claims 1, 4, 7, 8, and 54-63 are anticipated under 35 U.S.C. § 102(e) by Lipovsek.

SUMMARY

In summary, we reverse the rejections under 35 U.S.C. § 103(a) and enter a new rejection under 35 U.S.C. § 102(e).

This decision contains a new ground of rejection under 35 U.S.C. § 101 pursuant to 37 C.F.R. § 41.50(b) (effective September 13, 2004, 69 Fed. Reg. 49960 (August 12, 2004), 1286 Off. Gaz. Pat. Office 21 (September 7, 2004)). 37 C.F.R. § 41.50(b) provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review."

37 C.F.R. § 41.50(b) also provides that the Appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

> (1) Reopen prosecution. Submit an appropriate amendment of the claims so rejected or new evidence relating to the claims so rejected, or both, and have the matter reconsidered by the Examiner, in which event the proceeding will be remanded to the Examiner ....
>
> (2) Request rehearing. Request that the proceeding be reheard under § 41.52 by the Board upon the same record ....

REVERSED, 37 C.F.R. § 41.50(b)

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